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Synthesis of CHF_2-substituted 3-azabicyclo[3.1.0]-hexanes by photochemical decomposition of CHF_2-pyrazolines†

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A practical synthesis of CHF_2-substituted 3-azabicyclo[3.1.0]hexanes was developed for the first time. The key step was photochemical decomposition of CHF_2-substituted pyrazolines. This protocol has the advantages of simple operation, and mild conditions, as well as excellent functional group tolerance, giving the desired products in moderate to excellent yields.

The 3-azabicyclo[3.1.0]hexyl ring system as a conformationally constrained bicyclic isostere for the piperidine motif displays diverse biological activities and great potential in the pharmaceutical industry.[1] Representative examples of this type of application are potent μ opioid receptor antagonist **1** for the

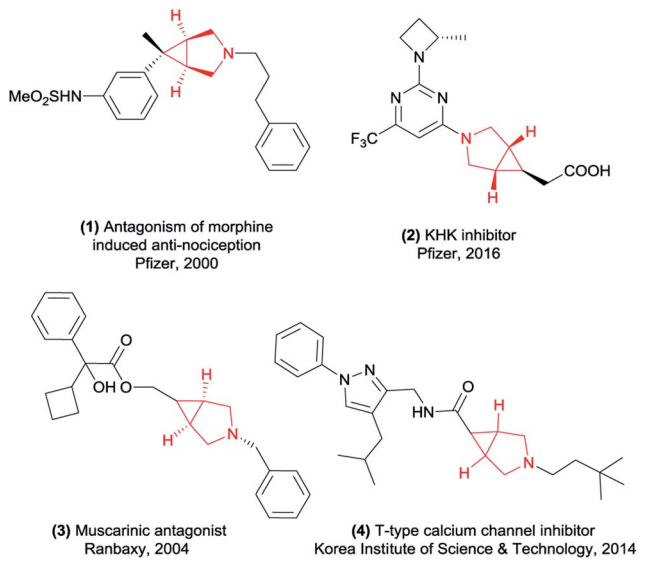
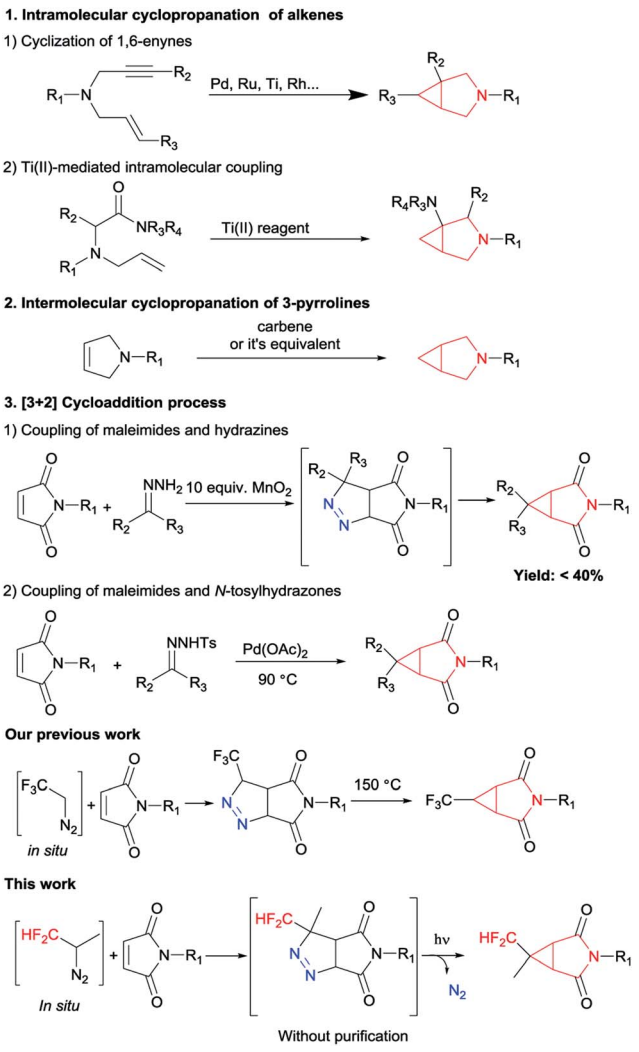


Fig. 1 Representative bioactive compounds with a 3-azabicyclo[3.1.0] hexane core structure.



Scheme 1 Construction of 3-azabicyclo[3.1.0]hexane scaffolds.

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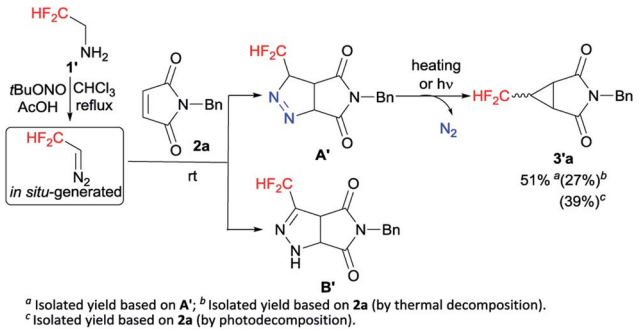
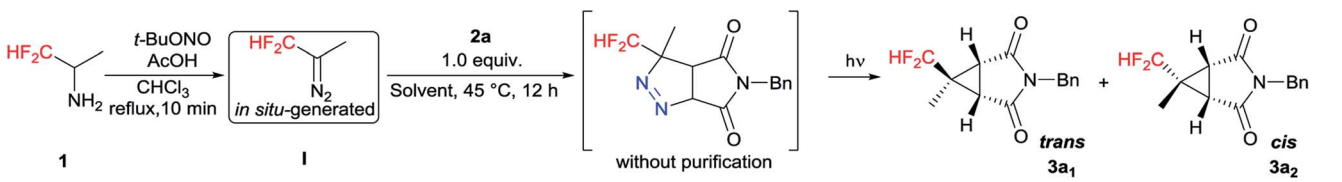


Scheme 2 Synthesis of 3-benzyl-6-difluoromethyl-3-azabicyclo [3.1.0]hexane-2,4-dione.

treatment of pruritus,[2] the ketohexokinase (KHK) inhibitor **2** for the treatment of non-alcoholic fatty liver disease (NAFLD),[3] muscarinic receptor antagonist **3** (ref. 4) and T-type calcium channel inhibitor **4** (ref. 5) (Fig. 1). In this context, considerable effort has been devoted to developing general and efficient methods for the synthesis of the 3-azabicyclo[3.1.0]hexane scaffolds (Scheme 1). The elegant early studies focused on the intramolecular cyclopropanation, such as metal-catalyzed oxidative cyclization of 1,6-enynes[6] and cyclopropanation of *N*-allylamino acid dimethylamides using Ti(II) reagents.[7] Furthermore, the intermolecular cyclization of 3-pyrrolines and metal carbenoids was also a useful tool to construct this core structure.[8] Although these known procedures had their merits, they were also associated with some drawbacks. For example, requiring long routes for the starting materials preparation and/or using expensive metal catalytic systems. In the last few years, [3 + 2] cycloaddition process has been the most popular method to construct this cyclopropane ring of 3-azabicyclo[3.1.0] hexanes. The coupling of maleimides and hydrazines has been reported by Lunn's group.[9] And Jiang and co-workers have disclosed a method of palladium-catalyzed cyclopropanation of maleimides and *N*-tosylhydrazones.[10] To match the increasing scientific and practical demands, it is still of continued interest and great importance to explore new and straightforward methods to access these highly rigid cyclopropanes with more simple operation.

On the other hand, decoration of organic molecules with fluorinated groups often affects their physicochemical and biological properties such as metabolic stability and lipophilicity,[11] so organofluorine compounds are widespread in pharmaceuticals, agrochemicals, and advanced functional materials. Among all fluorine-containing groups, difluoromethyl group can develop special effects on molecules: it can

Table 1 Optimization of the reaction conditions[a]



Entry	1 (equiv.)	*t*-BuONO (equiv.)	AcOH (equiv.)	Solvent	Lamp power (W)	Time (h)	Yield[b] (%) $3a_1$	Yield[b] (%) $3a_2$	dr[c]
1	2.0	2.4	0.4	Toluene	500	24	39	12	78 : 22
2	3.0	3.6	0.6	Toluene	500	24	51	14	78 : 22
3	4.0	4.8	0.8	Toluene	500	24	44	14	76 : 24
4	3.0	3.6	0.6	THF	500	24	29	13	69 : 31
5	3.0	3.6	0.6	DMSO	500	24	n.d.	n.d.	—
6	3.0	3.6	0.6	Et_2O	500	24	52	14	79 : 21
7	3.0	3.6	0.6	$(i\text{-}Pr)_2O$	500	24	36	12	75 : 25
8	3.0	3.6	0.6	i-PrOMe	500	24	51	14	78 : 22
9	3.0	3.6	0.6	MeCN	500	24	56	14	80 : 20
10	3.0	3.6	0.6	MeCN	400	24	50	16	76 : 24
11	3.0	3.6	0.6	MeCN	600	24	58	15	79 : 21
12	3.0	3.6	0.6	MeCN	800	24	61	16	79 : 21
13	3.0	3.6	0.6	MeCN	1000[d]	24	64	16	80 : 20
14	3.0	3.6	0.6	MeCN	1000	20	63	16	80 : 20
15	3.0	3.6	0.6	MeCN	1000	28	66	16	80 : 20
16	3.0	3.6	0.6	MeCN	1000	32	64	17	79 : 21

[a] Reaction conditions: a solution of 1-methyl-2,2-difluoroethanamine **1** in $CHCl_3$ and *t*-BuONO and HOAc were added in turn. After 10 min heating, the obtained yellow solution was cooled down to a room temperature by external water bath. Then **2a** was added into the reaction mixture and stirred at 45 °C. After removing $CHCl_3$, the residue was dissolved in 5 mL solvent and transferred into a quartz tube which was irradiated with a high-pressure mercury lamp (250–720 nm). [b] Isolated yield by chromatography on silicagel. [c] Diastereomeric ratio of $3a_1$ and $3a_2$ was based on column chromatography. [d] This is the maximum power of this lamp.

be used as a bioisostere of a carbinol moiety and as a more lipophilic hydrogen bond donor.[12] However, protocols for the synthesis of difluoromethylated azabicyclo[3.1.0]hexanes remain to be underexplored. In line with previous work from our group dealing with the preparation of difluoromethyl-substituted pyrazolines using *in situ* generated difluoromethyl diazomethane,[13] we report herein the development of a simple and efficient method to synthesize CHF_2-substituted 3-azabicyclo[3.1.0]hexane derivatives from commercially available maleimides.

Following our previously established protocol,[14] we initially examined the thermal decomposition of pyrazoline **A′**, and the desired **3′a** was observed in 51% yield, but **3′a** was obtained only in 27% yield based on 1-benzyl-1*H*-pyrrole-2,5-dione **2a** (see Scheme S1 and S2†). Considering the low yield and the tedious operation, we tried to develop a one-pot cascade approach (see Table S1†). Accidentally, we discovered that photochemical process was more effective than thermal decomposition. As we all know, photochemistry is considered as one of the simplest manifolds of chemical reactivity and photochemical reactions are the key for the synthesis of many reactive intermediates.[15] Accordingly, this phenomenon attracted our attention. On the other hand, considering the quantitative formation of the isomeric Δ^2-pyrazoline **B′** in the [3 + 2] cycloaddition process, we decided to prevent the formation of the byproduct **B′** by taking the simplest higher homologue – $CF_2H(CH_3)CNH_2$ (Scheme 2).

Initial tests were done on $CF_2H(CH_3)CHN_2$ **I** generated *in situ* and 1-benzyl-1*H*-pyrrole-2,5-dione **2a** as the model substrates.[16] To our delight, both *trans* (**3a$_1$**) and *cis* (**3a$_2$**) products were isolated separately and the yields of **3a$_1$** and **3a$_2$** were 39% and 12%, respectively (Table 1, entry 1). The stereochemistry was determined on the basis of the results from NMR spectroscopy (see Fig. S1†), and an example of which was shown for **3a$_1$** in Fig. 2. The bridgehead protons were correlated through space to the nearby difluromethyl protons, indicating they were on the same convex side of the bicyclic system. Encouraged by this result, we further optimized the reaction conditions, and the results were showed in Table 1. When the amount of **1** was increased to 3.0 equiv., increasing yield of **3a** was obtained, but further increases resulted in dramatically decreasing yield (entries 2 and 3). Further examination of the solvents indicated that MeCN was the optimum solvent, and the other solvents, such as THF, DMSO·Et_2O, $(i\text{-}Pr)_2O$ and i-PrOMe gave inferior results (entries 4–8). When MeCN was used as the solvent, the desired products **3a$_1$** and **3a$_2$** were produced in 56% and 14% yields, respectively. Lamp power was also a crucial factor in this system. Increasing the lamp power to 1000 W could significantly promote the result of this reaction, and the total yield of **3a** could reach to 80% (entries 10–13). At the same time, the reaction time was optimized (entries 14–16), and 28 hours was found to be optimum affording **3a$_1$** and **3a$_2$** in 66% and 16%, respectively. The experimental results also revealed that changing the reaction conditions had little effect on the diastereomeric ratio.

With the optimized reaction conditions in hand, the generality of maleimides in this cyclopropanation reaction was examined, and the results were summarized in Table 2. It was

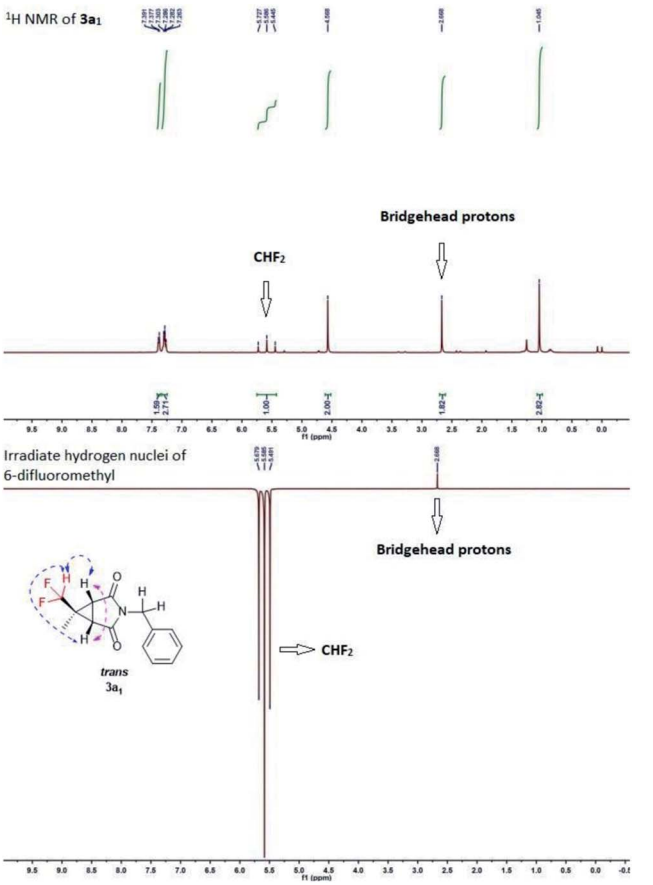


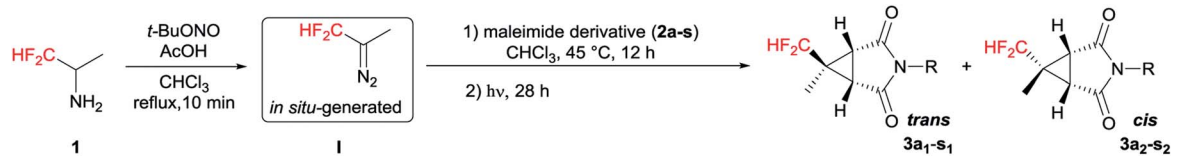
Fig. 2 NOESY of **3a$_1$** (irradiate hydrogen nuclei of 6-difluoromethyl).

worth mentioning that both of the diastereoisomers could be easily isolated by silica gel chromatography. Benzyl, *p*-methoxybenzyl and phenylethyl groups were compatible with the present conditions, obtaining excellent to good yields and diastereoselectivity (**3a$_1$–c$_1$** and **3a$_2$–c$_2$**). Various electron-donating (**2e**, **2g**, **2j**, **2m**) and electron-withdrawing groups (**2f**, **2h**, **2i**, **2k**, **2l**) at the different positions on the phenyl ring of maleimides **2** were fully tolerated. For instance, 1-(3,5-dimethoxyphenyl)-1*H*-pyrrole-2,5-dione (**2m**) gave the diastereoisomers **3m$_1$** and **3m$_2$** in 56% and 19% yields, respectively. And we were pleased to observe that a number of maleimides having alkyl substituents at the N-position were highly facile to afford the desired N-protected products (**3o$_1$–s$_1$** and **3o$_2$–s$_2$**) in good yields and diastereoselectivity. For example, *N*-(*n*-propyl) maleimide **2o** was 71% in yield and 68 : 32 in diastereomeric ratio.

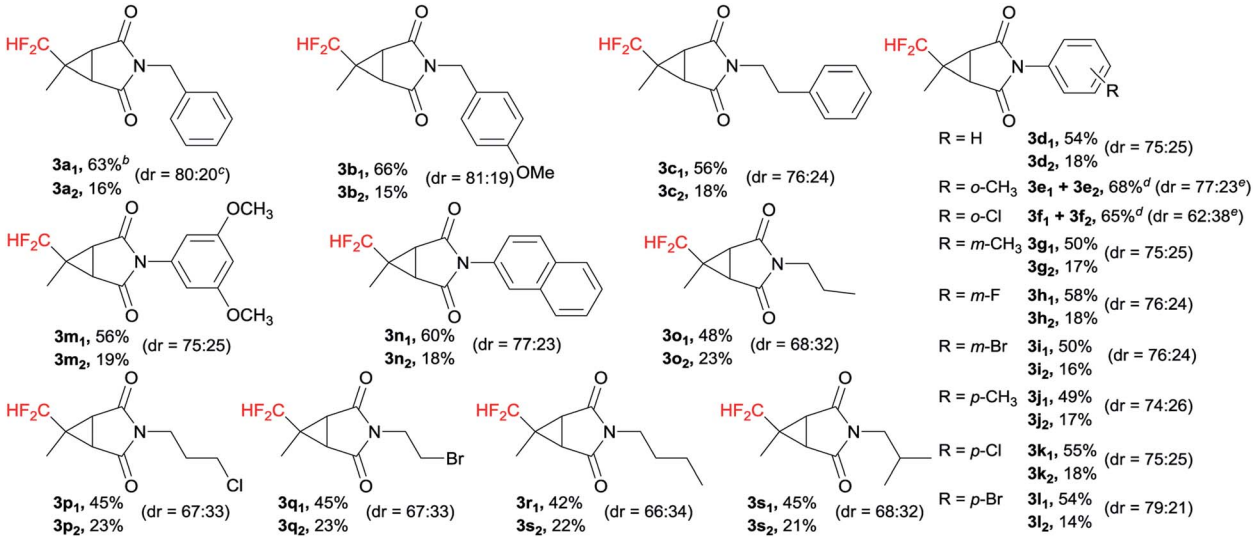
We further explored its application for the synthesis of the 3-azabicyclo[3.1.0]hexane scaffold. To our satisfaction, the representative reduction of the carbonyl groups in **3a$_1$** with $LiAlH_4$ in diethyl ether smoothly gave the pyrrolidine **4a$_1$** in nearly quantitative yield (Scheme 3).[14] It is worth mentioning that no cyclopropane ring cleavage was observed during this reaction.

Based on the experimental results and the previous literature,[17] a plausible mechanistic pathway is depicted in Scheme 4 with **2a** as a model substrate. Mechanistically, [3 + 2] cycloaddition is carried out with $CF_2H(CH_3)CHN_2$ and **2a** to generate

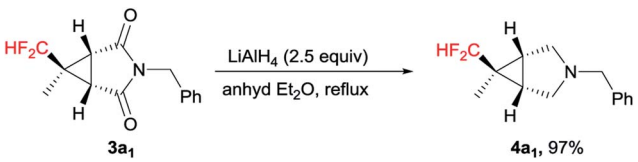
Table 2 Scope of substrates[a]



1 I $3a_1$-s_1 $3a_2$-s_2

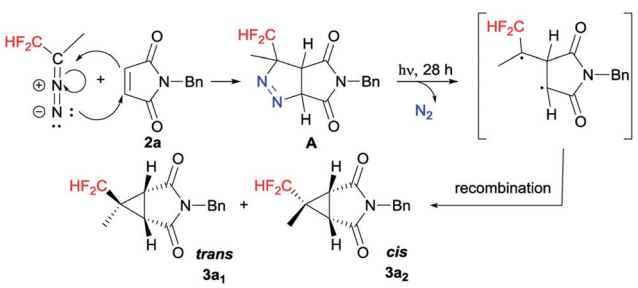


[a] Reaction conditions: a solution of 1-methyl-2,2-difluoroethanamine **1** (0.1 M, 3.0 eq.) in $CHCl_3$ and *t*-BuONO (3.6 eq.) and HOAc (0.6 eq.) were added in turn. After 10 min heating, the obtained yellow solution was cooled down to a room temperature by external water bath, and **2** (1.0 eq.) was added immediately. The reaction mixture was stirred at 45 °C for 12 h. After removing $CHCl_3$, the residue was dissolved by acetonitrile (5 mL) and transferred into a quartz tube which was irradiated with a 1000 W high-pressure mercury lamp for 28 h. [b] Isolated yield. [c] Diastereomeric ratio of *trans* and *cis* products was based on column chromatography. [d] Isolated yield combined *trans* and *cis* products. [e] Diastereomeric ratio was based on ^{1}H NMR.



Scheme 3 Synthesis of 3-azabicyclo[3.1.0]hexane $4a_1$.

pyrazoline **A**. Subsequently the photodenitrogenation of pyrazoline occurs by the stepwise cleavage of the two C–N=N–C bonds to give a 1,3-biradical. Finally, the 1,3-biradical recombines to give cyclopropane diastereoisomers $3a_1$ and $3a_2$.



Scheme 4 Proposed mechanism.

In summary, we have developed a general and efficient method for the synthesis of CHF_2-substituted 3-azabicyclo[3.1.0] hexane derivatives *via* photochemical process of commercially available maleimides and *in situ* generated $CF_2H(CH_3)CHN_2$. It is worth mentioning that both of the diastereoisomers could be easily isolated by silica gel chromatography. This protocol has the advantages of simple operation, mild conditions as well as excellent functional group tolerance. We believe that this method will expand the synthetic arsenal in the field of medicinal chemistry, agrochemistry and organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) T. A. Blizzard, F. DiNinno, J. D. Morgan 2nd, H. Y. Chen, J. Y. Wu, C. Gude, S. Kim, W. Chan, E. T. Birzin, Y. T. Yang,

L. Y. Pai, Z. Zhang, E. C. Hayes, C. A. DaSilva, W. Tang, S. P. Rohrer, J. M. Schaeffer and M. L. Hammond, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3861; (*b*) G. Lunn, L. R. Roberts, S. Content, D. J. Critcher, S. Douglas, A. E. Fenwick, D. M. Gethin, G. Goodwin, D. Greenway, S. Greenwood, K. Hall, M. Thomas, S. Thompson, D. Williams, G. Wood and A. Wylie, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 2200; (*c*) A. R. Renslo, H. Gao, P. Jaishankar, R. Venkatachalam, M. Gomez, J. Blais, M. Huband, J. V. Vara Prasad and M. F. Gordeev, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1126; (*d*) S. P. Runyon, C. M. Kormos, M. G. Gichinga, S. W. Mascarella, H. A. Navarro, J. R. Deschamps, G. H. Imler and F. I. Carroll, *J. Org. Chem.*, 2016, **81**, 10383; (*e*) L. M. Simpkins, S. Bolton, Z. Pi, J. C. Sutton, C. Kwon, G. Zhao, D. R. Magnin, D. J. Augeri, T. Gungor, D. P. Rotella, Z. Sun, Y. Liu, W. S. Slusarchyk, J. Marcinkeviciene, J. G. Robertson, A. Wang, J. A. Robl, K. S. Atwal, R. L. Zahler, R. A. Parker, M. S. Kirby and L. G. Hamann, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6476; (*f*) Z. Xiang, A. D. Thompson, J. T. Brogan, M. L. Schulte, B. J. Melancon, D. Mi, L. M. Lewis, B. Zou, L. Yang, R. Morrison, T. Santomango, F. Byers, K. Brewer, J. S. Aldrich, H. Yu, E. S. Dawson, M. Li, O. McManus, C. K. Jones, J. S. Daniels, C. R. Hopkins, X. S. Xie, P. J. Conn, C. D. Weaver and C. W. Lindsley, *ACS Chem. Neurosci.*, 2011, **2**, 730.

2 S. F. McHardy, S. D. Heck, S. Guediche, M. Kalman, M. P. Allen, M. H. Tu, D. K. Bryce, A. W. Schmidt, M. Vanase-Frawley, E. Callegari, S. Doran, N. J. Grahame, S. McLean and S. Liras, *Med. Chem. Commun.*, 2011, **2**, 1001.

3 M. Dowling, D. Fernando, K. Futatsugi, K. Huare, T. V. Magee, B. Raymer, A. Smith, B. Thuma, A. Tsai and M. H. Tu, *US pat.* 20170183328, 2017Chem. Abstr., 2017, 167, 151561m.

4 A. Ray, S. G. Dastidar, R. Shirumalla and S. Malhotra, WO patent 2007045979, 2007Chem. Abstr., 2007, 146, 468545m.

5 J. H. Kim and G. Nam, *Bioorg. Med. Chem.*, 2016, **24**, 5028.

6 (*a*) W. F. Wang, J. M. Yang, F. J. Wang and M. Shi, *Organometallics*, 2011, **30**, 3859; (*b*) F. Monnier, B. C. Vovard-Le, D. Castillo, V. Aubert, S. Derien, P. H. Dixneuf, L. Toupet, A. Ienco and C. Mealli, *J. Am. Chem. Soc.*, 2007, **129**, 6037; (*c*) D. Qian and J. Zhang, *Chem. Commun.*, 2011, **47**, 11152; (*d*) W. Wang, J. Yang, F. Wang and M. Shi, *Organometallics*, 2011, **30**, 3859; (*e*) Z. Zhang and M. Shi, *Eur. J. Org. Chem.*, 2011, **2011**, 2610.

7 (*a*) R. F. Boswell and R. G. Bass, *J. Org. Chem.*, 1977, **42**, 2342; (*b*) T. Kimura, N. Wada, T. Tsuru, T. Sampei and T. Satoh, *Tetrahedron*, 2015, **71**, 5952.

8 (*a*) B. Cao, D. Xiao and M. M. Joullie, *Org. Lett.*, 1999, **1**, 1799; (*b*) M. Gensini, S. I. Kozhushkov, D. S. Yufit, J. A. K. Howard, M. Es-Sayed and A. de Meijere, *Eur. J. Org. Chem.*, 2002, 2499.

9 G. Lunn, B. J. Banks, R. Crook, N. Feeder, A. Pettman and Y. Sabnis, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4608.

10 P. Chen, C. Zhu, R. Zhu, Z. Lin, W. Wu and H. Jiang, *Org. Biomol. Chem.*, 2017, **15**, 1228.

11 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*b*) S. D. Halperin, D. Kwon, M. Holmes, E. L. Regalado, L. C. Campeau, D. A. DiRocco and R. Britton, *Org. Lett.*, 2015, **17**, 5200; (*c*) J. Miao, K. Yang, M. Kurek and H. Ge, *Org. Lett.*, 2015, **17**, 3738; (*d*) D. O'Hagan, *J. Fluorine Chem.*, 2010, **131**, 1071; (*e*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.

12 Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797.

13 J. Li, X. L. Yu, J. Cossy, S. Y. Lv, H. L. Zhang, F. Su, P. K. Mykhailiuk and Y. Wu, *Eur. J. Org. Chem.*, 2017, **2017**, 266.

14 O. S. Artamonov, E. Y. Slobodyanyuk, O. V. Shishkin, I. V. Komarov and P. K. Mykhailiuk, *Synthesis*, 2013, **45**, 225.

15 (*a*) A. V. Denisenko, T. Druzhenko, Y. Skalenko, M. Samoilenko, O. O. Grygorenko, S. Zozulya and P. K. Mykhailiuk, *J. Org. Chem.*, 2017, **82**, 9627; (*b*) C.-C. Wang, Y.-C. Ku and G. J. Chuang, *J. Org. Chem.*, 2015, **80**, 10979; (*c*) A. M. Linsenmeier, C. M. Williams and S. Brase, *J. Org. Chem.*, 2011, **76**, 9127.

16 Firstly, $CF_2H(CH_3)CHN_2$ **I** was prepared by 2.0 mmol $CF_2H(CH_3)CHNH_2$ **1**, based on our previous work. 13 Subsquently, **2a** (1.0 mmol) was added and the reaction mixture was stirred at 45 °C for 12 h. After removing $CHCl_3$, the residue was dissolved by toluene (5 mL) and transferred into a quartz tube which was irradiated with a 500 W high-pressure mercury lamp (250–720 nm). See ESI† for more details.

17 (*a*) S. Shiraki, C. S. Vogelsberg and M. A. Garcia-Garibay, *Photochem. Photobiol. Sci.*, 2012, **11**, 1929; (*b*) M. Abe, J. Ye and M. Mishima, *Chem. Soc. Rev.*, 2012, **41**, 3808; (*c*) L. Mertens and R. M. Koenigs, *Org. Biomol. Chem.*, 2016, **14**, 10547.

